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Examiner Answer to Appeal Brief

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_____ CLMPTO ____
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Examiner Search Notes

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File Wrapper Search Info

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Sequence Problem Att. from Examiner

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Office Action Summary	Application No.	Applicant(s)	
	10/009,247	KRAUSE ET AL.	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/31/03;12/05/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are pending. Claims 1-17 are rejected.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claim 14, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the sample" in line 1. There is insufficient antecedent basis for this limitation in the claim. This could be corrected by adding "in a sample" after the words – an enzyme – in line one.

Claim 1 is also confusing because it recites the phrase "at least part of which is covered with a layer of a biodegradable polymer" in the second line. It is unclear whether this modifies the substrate or the sample.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5-9, 11, 16, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Saum, et al., Use of Substrate Coated Electrodes and AC Impedance Spectroscopy for the Detection of Enzyme Activity, Biosensors and Bioelectronics, Vol. 13, March 15, 1998, pp. 511-518.

Saum discloses a method of utilizing the catalytic activity of a protease to form the basis of an electrochemical sensor, which detects erosion of a surface layer of a protein by the enzyme (pg. 512, col. 1, third full para.). Gelatin (biodegradable polymer), is coated on the electrodes (substrate) and after immersion of the coated electrodes in a collagenase solution (enzyme) the impedance is measured at timed intervals (pg. 513, sects. 2.3 and 2.5). The AC impedance, measured with an alternating voltage or current, is a combination of both the resistive and capacitive properties of a material (pg. 511, vol. 2, lines 12-14). Differences in the concentrations of collagenase can be detected (pg. 515, fig. 3). The detection of low concentrations of enzyme can be improved by stirring the solution (pg. 516, sect. 3.3).

Claims 1-2, 7-8, 10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Ward (WO 89/09937).

Ward discloses a biologically modified quartz crystal microbalance (BMQMC) sandwiched between two electrodes, adsorbed onto one surface of the electrode is a capture reagent bound thereto a solution containing an analyte, which will be bound to the adsorbed capture reagent, thus forming a bound complex (pg. 6). Ward additionally discloses the QCM is then contacted with a conjugate comprising anti-analyte reagent and an enzyme. Ward further discuses the QCM, having the conjugate bound thereto, is then contacted with a solution containing a substrate, which is specific for the enzyme, which will then catalyze a reaction in which the substrate is converted to a product P, that is insoluble and precipitable on the BMQCM surface, thereby leading to a change in mass and hence a change in resonance frequency, as measured by an external circuit (pg. 7). Moreover, Ward discloses, suitable analytes include proteins, hormones, enzymes, antibodies, drugs, carbohydrates, nucleic acts and examples of the enzyme substrate system include alkaline phosphates and 5-bromo-4-cloro-inolylphosphte (BCIP) and illustrative polymer surfaces are polystyrene redox polymer films such as polyvinylferrocen, PV-Fc, which serve as hydrophobic layers to enhance binding to capture the reagent, as well as reactive layers that react wit the enzymatic reaction product, leading to an increased mass and changed resonant frequency (pg. 9). Finally, Ward discloses that suitable layers for the embodiments shown in Figs. 2 and 3 comprise organic thin films, redox polymers and conducting polymers which are capable of incorporating anions upon oxidations, i.e. the substrates is a transducer/electrode and more specifically and electrochemical transducer by definition.[1]

[1] Many biocatalyic reactions, especially those of oxidoreductases, hydrolases, and lysases, are associated with the consumption or formation of electroactive substrates or products in concentrations proportional to the analyte concentration and for this reason most commercially available biosensors are enzyme sensors based on electrochemical transducers. Pg. 4. Typical electrochemically detectable (co-) substrates and products include

Claims 1, 5-9 and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Athey, et al. (5,846,744).

Athey discloses a method based on impedance analysis of polymer coatings of electrodes where the polymer layer becomes porous and causes a measurable change in electrical properties of the electrode surface to detect the presence of an enzyme through the reliance on the occurrence of an enzymatic reaction that creates changes in the impedance of the electrode as a result of the partial or complete removal of an insulating polymer film from its surface (can increase current at the polarized electrode, produce a product which can react with the polymer or can directly hydrolyze the polymer membrane (col. 2, lines 41-63, Fig. 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saum, et al., Use of Substrate Coated Electrodes and AC Impedance Spectroscopy for the Detection of Enzyme Activity, Biosensors and Bioelectronics, Vol. 13, March 15, 1998, pp. 511-518 and/or Ward (WO 89/09937) and/or Athey, et al. (5,846,744) in view of Sigl, et al., Assembly of

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oxygen, hydrogen peroxide, hydrogen ion, ammonia, carbon dioxide, reduce or oxidized cofactors, and redox-active (oxidized or reduce) prosthetic groups in oxidoreductases, all of which can easily be converted into electrical signals by suitable transducers (e.g. amperometric or potentiometric electrodes or conductometric sensors or mediator-modified redox electrode). Pg. 4 See Katerkamp, et al., Chemical and Biochemical Sensors, Ullman's Encyclopedia of Industrial Chemistry, 2002, pp1-23. In our case, the organic redox polymer and thin films create the mediator modified redox electrode for example.

polymer/lipid composite films of solids based on hairy rod LB-film, European BioPhysics Journal, Vol. 25, 1997, pp. 249.

Saum and Ward and Athey disclose as set forth above. Ward further discloses the use of QMC. However, neither Saum nor Athey specifically disclose the use of QMC and Saum, Ward nor Athey specifically disclose the use of surface plasmon resonance, or ellipsometry. Saum further discloses that the development of an efficient sensing system to detect aerosolized enzymes into the workplace, which can measure the amount of proteases in solution could be useful for incorporation in an air sampler of for other process liquid measurements to give real-time measurements. Pg. 511. Ward discloses that there is a need for better sensitivity and detection limits for specific binding assays in order for more reliable assays. Pg. 4. Athey further discloses that the concept of sensors based on an electrochemical transducer sensitized with a biological moiety, such as an enzyme, is both simple and elegant and offers the prospect of reagentless clinical analysis with minimum sample preparation resulting in ease of operation, thus obviating the requirement for trained laboratory personnel and deployment of sensors in decentralized laboratories, which would facilitate a more rapid return of clinical information to the clinician and institution of earlier therapy. (col. 1). Sigl discloses that quartz crystal microbalance, ellipsometry, and surface plasmon resonance, all permit the utilization of polymer/lipid composite films and are detection methods well known in the field of biosensors (pg. 249-250). Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to have utilized any one of the detection methods taught in Sigl in Saum and/or Ward and/or Athey because they are all well known detection method in the filed of biosensors and therefore would have been obvious to select among them. See also MPEP 2144.06.

Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saum, et al., Use of Substrate Coated Electrodes and AC Impedance Spectroscopy for the Detection of Enzyme Activity, Biosensors and Bioelectronics, Vol. 13, March 15, 1998, pp. 511-518 and/or Ward (WO 89/09937) and/or Athey, et al. (5,846,744) in view of Franssen, et al., Enzymatic degradation of cross-linked dextrans, Macromolecules, Vol. 32, no. 9, May 4, 1999, pp. 2896-2902 (Abstract) and Shalaby, et al., Synthesis of enzyme-digestible, interpenetrating hydrogel networks by gamma-irradiation, Journal of Bioactive and Compatible Polymers, Vol. 8, No. 1, 1993, pp. 3-23 (Abstract).

Saum and Ward and Athey disclose as set forth above. Ward further discloses the use of QMC. However, neither Saum nor Athey specifically disclose the use of QMC and Saum, Ward nor Athey specifically disclose the use of surface plasmon resonance, or ellipsometry. Saum further discloses that the development of an efficient sensing system to detect aerosolized enzymes into the workplace, which can measure the amount of proteases in solution could be useful for incorporation in an air sampler of for other process liquid measurements to give real-time measurements. Pg. 511. Ward discloses that there is a need for better sensitivity and detection limits for specific binding assays in order for more reliable assays. Pg. 4. Athey further discloses that the concept of sensors based on an electrochemical transducer sensitized with a biological moiety, such as an enzyme, is both simple and elegant and offers the prospect of reagentless clinical analysis with minimum sample preparation resulting in ease of operation, thus obviating the requirement for trained laboratory personnel and deployment of sensors in decentralized laboratories, which would facilitate a more rapid return of clinical information to the clinician and institution of earlier therapy. (col. 1). Franssen discloses that dextran hydrogels

are enzymatically degraded by dextranse to demonstrate that the degradation can be divided into two processes. Shalaby discloses that albumin –crosslinked poly(vinylpyrrolidone) hydrogel are degraded in the presence of pepsin. Yashuda discloses that poly(ester-carbonates are effectively biodegraded by lipoprotein lipase and generated numerous cavities on the outermost surface of polymer films. Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to have utilized known enzyme/substrate pairs in Saum or Ward or Athey because choosing an enzyme and a suitable substrate lies within the ordinary skill of one in the art and each of those enzyme substrate pairs are known to interact with one another to give the results, i.e. the ability to produce a signal through degradation.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saum, et al., Use of Substrate Coated Electrodes and AC Impedance Spectroscopy for the Detection of Enzyme Activity, Biosensors and Bioelectronics, Vol. 13, March 15, 1998, pp. 511-518 and/or Ward (WO 89/09937) and/or Athey, et al. (5,846,744) in view of Frickey, et al. (4,670,381).

Saum and Ward and Athey disclose as set forth above. Ward further discloses the use of QMC. However, neither Saum nor Athey specifically disclose the use of QMC and Saum, Ward nor Athey specifically disclose the use of surface plasmon resonance, or ellipsometry. Saum further discloses that the development of an efficient sensing system to detect aerosolized enzymes into the workplace, which can measure the amount of proteases in solution could be useful for incorporation in an air sampler of for other process liquid measurements to give real-time measurements. Pg. 511. Ward discloses that there is a need for better sensitivity and detection limits for specific binding assays in order for more reliable assays. Pg. 4. Athey further discloses that the concept of sensors based on an electrochemical transducer sensitized with a

biological moiety, such as an enzyme, is both simple and elegant and offers the prospect of reagentless clinical analysis with minimum sample preparation resulting in ease of operation, thus obviating the requirement for trained laboratory personnel and deployment of sensors in decentralized laboratories, which would facilitate a more rapid return of clinical information to the clinician and institution of earlier therapy. (col. 1). Frickey discloses competitive binding immunoassays, i.e. bringing a sample to be detected for the presence of an analyte into contact with a substrate, which contains binding sites for the analyte, in the presence of a conjugate of the analyte and an enzyme label – and detecting the presence of unbound conjugate. Col. 1. Frickey additionally discloses that competitive binding immunoassays take advantage of natural immunological reactions have found widespread use as analytical techniques in clinical chemistry and that because of the specificity of the reactions, these assays are particularly advantageous in quantifying biological analytes which are present in very low concentration and cannot be adequately quantitated by chemical techniques. Moreover, Frickey discloses the use of polymers and organo-polymers and detection utilizing radiometric, fluorometric or spectrophotometric apparatus using generally known procedures. Cols. 4-10. Thus, it would have been obvious to one of ordinary skill in the art to have utilized a competitive binding immunoassay as taught in Frickey in Saum and/or Ward and/or Athey for the specific reasons set forth above and because it is a well known alternative use (a standard immunoassay using competition between an enzyme-labeled analyte-analog and the analyte and the analyte can being detected can even be another enzyme as taught by Frickey), being combined with a method of detection and as such would have been obvious to one of ordinary skill in the art to have utilized such an assay.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Donel Leech, Affinity Biosensors, Chemical Society Reviews, Vol. 23, No. 3, 1994, pp.205-213 discloses recent advances in the development and application of biosensors, including the ability to incorporate immobilized biological receptor molecules that can reversibly detect receptor-ligand interactions with high differential selectivity and in a non-destructive fashion and includes competitive binding affinity systems.

Han, et al., Selective monitoring of peptidase activities with synthetic polypeptide substrates and polyion-sensitive membrane electrode detection, FASEB Journal, Vol. 10, No. 14, 1996, pp. 1621-1626, discloses monitoring peptidase activities in a biological sample based on the design of synthetic polypeptide substrates, i.e. polymer films, recognized specifically by the peptidase to be determined.

Chen, et al., Dynamic Surface Events Measured by Simultaneous Probe Microscopy and Surface Plasmon Detection, Analytical Chemistry, Vol. 68, No. 8, April 15, 1996, pp. 1451-1455, discloses utilizing SPR in biomedical research of polymer surface degradation, i.e. interfacial erosion of a biodegradable polymer which undergoes surface-mediated acid-catalyzed hydrolysis, and surface adsorption phenomena, i.e. the dynamic adsorption of a plasma protein to a polymeric interface in the field of biosensors, including the study of receptor-ligand association and the design of thin-film technologies.

McNeil, et al., Electrochemical Sensors Based on Impedance Measurement of Enzyme-Catalyzed Polymer Dissolution: Theory and Applications, Analytical Chemistry, Vol. 67, No.

21, November 1, 1995, pp. 3928-35, discloses utilizing impedance measurement of capacitance changes produced during enzyme-catalyzed dissolution of polymer coating on electrodes through the action of urease. The amount of urease labeled bound to the membranes was assessed by both impedance and spectrophotometric measurements.

Rickert, et al., Quartz crystal microbalances for quantitative biosensing and characterizing protein multilayers, Biosensors & Bioelectronics, Vol. 12, no. 7, 1997, pp. 567-575, discloses that QCMs are suitable transducers for chemical and biochemical sensing in general and that recent advances in overlay preparation and transducer electronic made possible the sensitive operation in liquids for qualitative studies of a variety of affinity reactions.

Arwin, Spectroscopic ellipsometry and biology: recent developments and challenges, Thin Solid Films, Vols. 313-314, 1998, pp. 764-774, discloses that single wavelength ellipsometry can be used in the areas of macromolecular adsorption on solid surfaces and that the results contribute significantly to the understanding of the basic mechanisms of adsorption and surface dynamics of proteins. Arwin further discloses ellipsometrically based biosensor systems, which contain coatings.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer Ione Harle
August 17, 2004

MICHAEL MELLER
PRIMARY EXAMINER